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Communication to the Editor

Preparation of Novel Hexythiazox Analogues

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Abstract: Novel analogues of the title compound were prepared in several steps: *via* addition of methylmagnesium iodide to an acetamide derivative to yield diastereomeric amino alcohols, followed by hydrolysis, cyclization to the corresponding oxazole or thiazole derivative, and a coupling reaction with isocyanates. Results from acaricidal tests showed the compounds to be 100 times less active than hexythiazox.

Key words: hexythiazox, acaricide, oxazolidine derivative, thiazolidine derivative

1 INTRODUCTION

Phytophagous mites (Acaridae) cause great losses in agricultural yield and quality. Their control is one of the main problems of crop protection. Hexythiazox (Table 1; **1a**) is a non-systemic acaricide virtually harmless to mammals and with no effect on beneficial insects and predators of mites. Nowadays, hexythiazox is widely used for chemical control of mites on cotton, fruit and vegetables.[1–6]

Our general interest in the synthesis of new potent acaricides prompted us to prepare novel analogues of hexythiazox. In this paper, we describe the synthesis and screening of a series of novel methyl-substituted analogs (Table 1; **1b–g**).

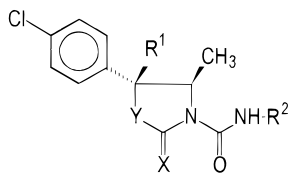
2 RESULTS AND DISCUSSION

The preparation of intermediates for the synthesis is detailed in Fig. 1. Addition of methylmagnesium iodide to the known acetamide derivative **2**[7] afforded a mixture of *syn* and *anti* isomers (**3a** and **3b**, respectively), which were not separated. Acid-catalyzed hydrolysis of the amide groups yielded a 2·5 : 1 mixture of stereoisomers.

The minor diastereomer (**4a**) was isolated in pure form by recrystallization from dry ethanol. Upon adding ether to the filtrate, the major isomer (**4b**) precipitated.

Reaction of the *syn* isomer (**4a**) with carbon disulfide in the presence of triethylamine followed by treatment

TABLE 1
Hexythiazox and Analogues Tested



1	*X*	*Y*	R^1	R^2
a	O	S	H	Cyclohexyl (Hexythiazox)
b	S	S	CH_3	Cyclohexyl
c	S	S	CH_3	Phenyl
d	O	S	CH_3	Cyclohexyl
e	O	S	CH_3	Phenyl
f	S	O	CH_3	Cyclohexyl
g	S	O	CH_3	Phenyl

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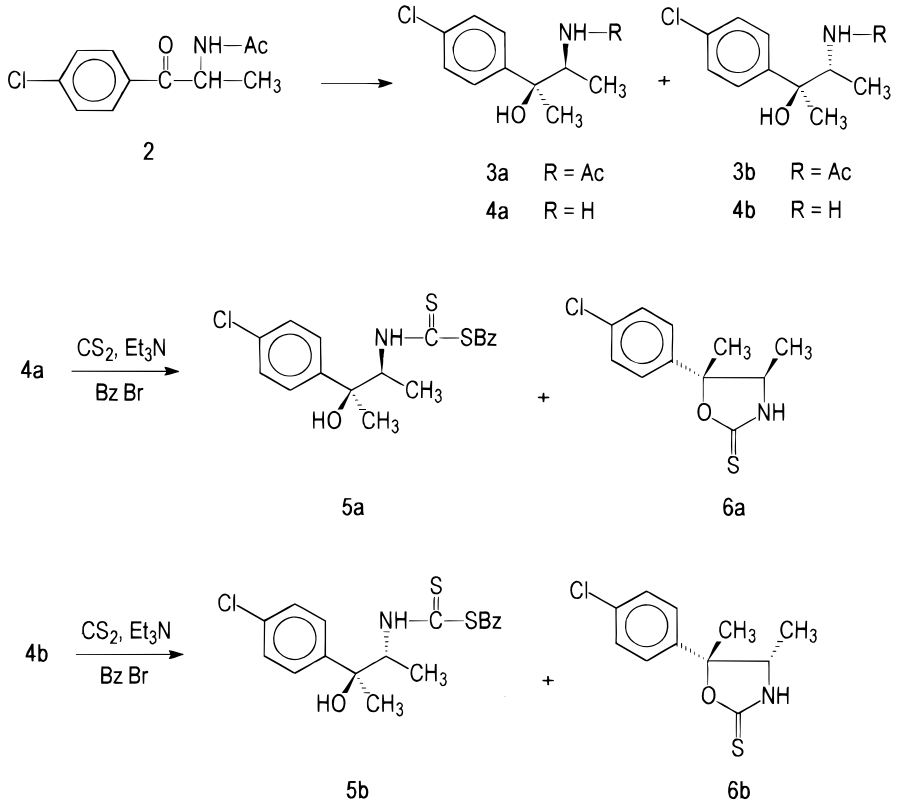

Fig. 1. Preparation of intermediates.

with benzyl bromide afforded a mixture of two compounds. Although the main product was found to be the dithiocarbamic acid derivative (**5a**), the oxazolidine derivative (**6a**) was also isolated.

Likewise, treatment of the *anti* isomer (**4b**) with carbon disulfide and benzyl bromide afforded **5b** and **6b** in a ratio of 2 : 1.

Furthermore, we found that **4a** and **4b** could be completely converted into **6a** and **6b** (respectively) by a longer treatment with carbon disulfide.

In contrast, the boron trifluoride diethyl etherate-catalyzed cyclization of both **5a** and **5b** afforded the same product, namely the *trans* thiazoline isomer, **7** (Fig. 2). This result confirmed that the cyclization followed an S_N1 mechanism to provide the thermodynamically more stable *trans* isomer (**7**). Acid-catalyzed hydrolysis of the latter afforded a 2 : 1 mixture of thiazolidine-2-one (**6c**) and thiazolidine-2-thione (**6d**) derivatives, which were separated by column chromatography.

The oxazolidine and thiazolidine derivatives (**6a–d**) were then readily converted into the corresponding hexythiazox analogues (**1b–g** and **10a**, **b**) by treatment with cyclohexyl isocyanate (**8**) or phenyl isocyanate (**9**) (Fig. 3).

The configurations of these new products (**6a–d**, **1b–g** and **10a**, **b**) have been assigned mainly on the basis of the chemical shifts observed for the methyl groups in their [^{1}H] and [^{13}C]NMR spectra. For instance, in the spectrum of the *cis* compound (**10a**) the peak attributed to the CH_3-4 was observed at higher field ($\delta = 0{\cdot}91$ ppm) than that of the corresponding *trans* isomer (**1f**; $\delta = 1{\cdot}52$ ppm), probably as a result of the interaction between the methyl group and the aromatic ring. Likewise, in the [^{13}C]NMR spectrum of the *trans* compound (**1f**), a decrease in the chemical shifts of methyl groups can be expected as the result of the repulsive interaction of their electron clouds. Compound **1f** displayed two signals at 15·39 ppm and 22·90 ppm, whereas **10a** gave signals at 16·94 ppm and 27·23 ppm. Furthermore, the situation was reversed for

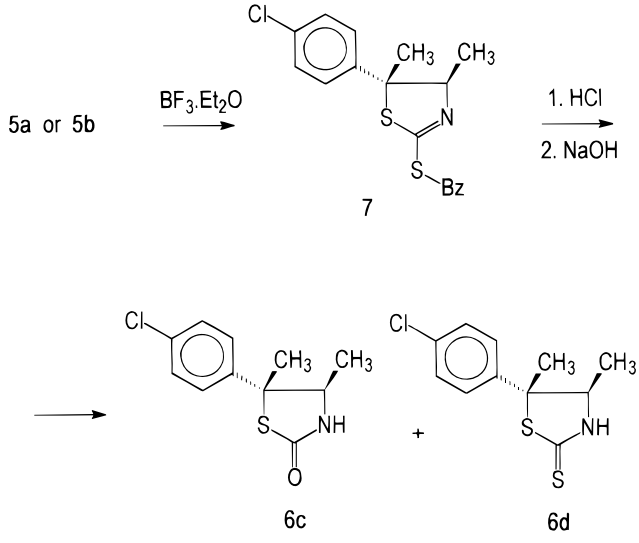

Fig. 2. Alternative preparation of intermediates.

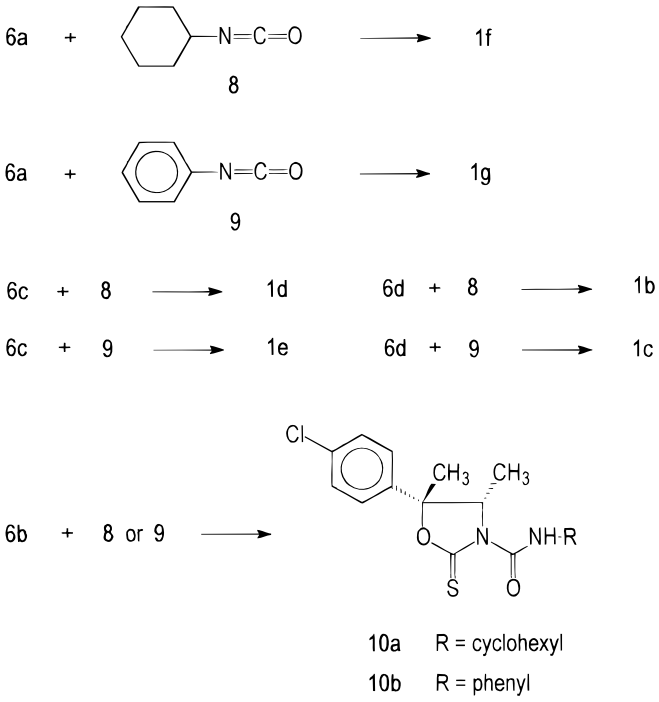

Fig. 3. Preparation of hexythiazox analogues.

the C-1″ resonance which was slightly more deshielded for the *cis* isomer (**10a**; $\delta = 136{\cdot}72$ ppm) than in the spectrum of the *trans* compound (**1f**; $\delta = 142{\cdot}13$ ppm). In the *cis* isomer, the methyl group and the phenyl group occupied near-planar positions and the methyl group exerted a stronger γ-gauche effect on the chemical shift in the C-1″ position.

The analogues **1b**–**g** of hexythiazox synthesized here were tested against spider mite (*Tetranychus urticae* Koch) by standard methods,[8] using hexythiazox as a reference compound. Although all compounds demonstrated appreciable acaricidal and ovicidal activity, they were 100 times less potent against this mite species than hexythiazox. Compounds **10a** and **10b** had no activity.

3 EXPERIMENTAL

Melting points were determined on a Büchi aparatus and are uncorrected. [^{1}H] and [^{13}C]NMR spectra measurements were carried out in deuterochloroform (except for **3a** and **3b**, where deuterochloroform/deuteromethanol was used), using a JEOL FX 100 FT-NMR spectrometer. All signals are expressed as δ values downfield from tetramethylsilane used as an internal standard. MS measurements were carried out with a Kratos MS-25 RFA combined GC/MS system (ionizing energy 70 eV, voltage 48 V). The silica gel used was obtained from Merck and that used for thin-layer chromatography was Kieselgel PF_{254}, whilst that employed for column chromatography was Kieselgel 60. All solvents were dried by means of standard methods, and most reactions were carried out under argon.

3.1 Preparation of compounds 3a and b, 4a and b, 5a and b, 6a–d, 7

3.1.1 N-[*2-(4-Chlorophenyl)-2-hydroxy-1-methylpropyl*]*acetamide* (***3***)

To a stirred solution of methylmagnesium iodide prepared from 3·2 g (0·13 g atom) of magnesium turnings and methyl iodide (15·8 g, 0·112 mol) in dry diethyl ether (50 ml), was added dropwise a solution of *N*-[2-(4-chlorophenyl)-1-methyl-2-oxoethyl]acetamide (**2**) in dry tetrahydrofuran (50 ml) at room temperature and the resulting suspension was stirred at reflux temperature for 2 h. After cooling, the reaction mixture was diluted with ether (100 ml) and then quenched by the addition of saturated ammonium chloride solution (100 ml). The organic layer was separated, the aqueous layer was extracted with ether (400 ml) and the combined organic solutions were dried over magnesium sulfate. Evaporation of the solvent gave a mixture of *syn* and *anti* isomers (**3a** and **3b**) which was purified by column chromatography with chloroform + methanol (95 + 5 by volume) as eluent. Yield 5·3 g (82%) white crystalline solid, m.p. 174–175°C. [^{1}H]NMR: 0·92 (d, $J = 8$ Hz, 3H, CH_3), 1·5 (s, 3H, CH_3), 2·02 (s, 3H, CH_3), 4·0–4·35 (m, 1H, CH), 5·9 (d–m, 1H, NH), 7·1–7·5 (m, 4H, aromatic H). MS: m/z (%) = 242(12) [$M^+ + H$].

3.1.2 *3-Amino-2-(4-chlorophenyl)butan-2-ol hydrochloride* (***4.HCl***)

To a suspension of **3** (5·3 g, 0·82 mol) in hydrochloric acid (1·5 M; 470 ml) was added ethanol and the resulting mixture was stirred at reflux temperature for 12 h. After evaporation of the solvents, the crude product was dried over phosphorus pentoxide and then dissolved in dry ethanol. After cooling, the resulting solid was filtered, washed with cold ethanol and dried under vacuum over phosphorus pentoxide to afford **4a.HCl** (1·06 g, 20%) as a colourless solid, m.p. 296–300°C. Free base [^{1}H]NMR: 0·82 (d, $J = 8$ Hz, 3H, CH_3), 1·51 (s, 3H, CH_3), 2·05 (m, 3H, exchangeable with D_2O, NH_2, OH), 3·1 (q, $J = 8$ Hz, CH), 7·35 (m, 4H, aromatic H).

The filtrate was diluted with dry ether and left to stand at room temperature. The precipitate was collected and washed with ether to give **4b.HCl** (2·65 g, 50%) as a white crystalline solid, m.p. 202°C. Free base [^{1}H]NMR: 1·20 (d, $J = 8$ Hz, 3H, CH_3), 1·52 (s, 3H, CH_3), 2·0 (m, 3H, OH, NH_2), 3·31 (q, $J = 8$ Hz, CH), 7·35 (m, 4H, aromatic H).

3.1.3 *Benzyl* syn-[*2-(4-chlorophenyl)-2-hydroxy-1-methylpropyl*]*dithiocarbamate* (***5a***) *and* trans-*5-(4-chlorophenyl)-4,5-dimethyloxazolidine-2-thione* (***6a***)

To a cold (0°C) suspension of **4a.HCl** (4·73 g, 20 mmol) and triethylamine (4·05 g, 40 mmol) in dry tetrahydrofuran (45 ml) was added carbon disulfide (1·68 g, 22 mmol) and the resulting mixture stirred at 15°C for

1 h. After cooling to 0°C, a solution of benzyl bromide (3·43 g, 20 mmol) in dry tetrahydrofuran (10 ml) was added dropwise and the resultant solution stirred at room temperature for 2·5 h. The triethylamine hydrochloride formed was filtered off, the solvent was evaporated under vacuum and the residue purified by column chromatography with hexane + ethyl acetate (9 + 1 by volume) as eluent to give 1·21 g (26%) of **6a**, followed by 4·51 g (63%) of **5a**. **5a**: m.p. 147–151°C. [^{1}H]NMR: 0·90 (d, J = 6 Hz, 3H, CH_3), 1·55 (s, 3H, CH_3), 2·05 (s, 1H, exchangeable with D_2O, OH), 4·5 (s, 2H, CH_2), 5·05 (m, 1H, CH), 7·1–7·5 (m, 9H, aromatic H).

6a: m.p. 163–165°C. [^{1}H]NMR: 1·3 (d, J = 6 Hz, 3H, CH_3), 1·70 (s, 3H, CH_3), 4·05 (q, J = 6 Hz, 1H, CH), 7·1–7·4 (m, 4H, aromatic H), 8·05 (br.s, 1H, NH).

3.1.4 Benzyl anti-[*2-(4-chlorophenyl)-2-hydroxy-1-methylpropyl*]*dithiocarbamate* (***5b***) *and* cis-*5-(4-chlorophenyl)-4,5-dimethyloxazolidine-2-thione* (***6b***)

According to the procedure described for the preparation of **5a** and **6a**, compound **4b.HCl** was treated with carbon disulfide to give **5b** and **6b** in 60% and 30% yields respectively. **5b**: m.p. 89–91°C. [^{1}H]NMR: 1·3 (d, J = 6 Hz, 3H, CH_3), 1·55 (s, 3H, CH_3), 2·0 (s, 1H, NH), 2·4 (s, 1H, exchangeable with D_2O, OH), 4·35 (s, 2H, CH_2), 5·0 (m, 1H, CH), 7·2–7·4 (m, 9H, aromatic H). MS: m/z (%) = 365(4) [M^+].

6b: m.p. 140–142°C. [^{1}H]NMR: 0·80 (d, J = 6 Hz, 3H, CH_3), 1·81 (s, 3H, CH_3), 4·02 (q, J = 6 Hz, 1H, CH), 7·1–7·5 (m, 4H, aromatic H), 8·5 (br.s, 1H, NH).

3.1.5 Direct conversion of ***4a*** *into* ***6a***

To a cold (0°C) suspension of **4a** (2·5 g, 11 mmol) in dry tetrahydrofuran (40 ml) was added triethylamine (3·1 ml), then carbon disulfide (1 ml) with stirring and the resulting mixture was stirred at room temperature for 24 h. The amine salt formed was filtered off, the solvent was evaporated under vacuum and the residue was purified by column chromatography on aluminium oxide (Brockman II, neutral) with ethyl acetate as eluent to yield 2·2 g (86%) of **6a**.

3.1.6 Direct conversion of ***4b*** *into* ***6b***

According to the procedure described for the preparation of **6a**, compound **4b** was converted into **6b** in 93% yield.

3.1.7 trans-*2-Benzylthio-5-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydrothiazole* (*7*)

To a stirred solution of **5a** (4·1 g, 11 mmol) in dry dichloromethane (80 ml) was added dropwise boron trifluoride diethyl etherate (16 ml) and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with dichloromethane (60 ml), washed successively with saturated sodium hydrogen carbonate solution and water, and then dried over magnesium sulfate. Evaporation of the solvent under vacuum gave an oil which was purified by column chromatography on aluminium oxide (Brockman II, neutral) with hexane + ethyl acetate (4 + 1 by volume) as eluent. Yield: 3·55 g (92%) as light-yellow solid, m.p. 70–72°C. [^{1}H]NMR: 1·28 (d, J = 7 Hz, 3H, CH_3), 1·69 (s, 3H, CH_3), 4·34 (s, 2H, CH_2), 4·43 (q, J = 7 Hz, 1H, CH), 7·1–7·6 (m, 9H, aromatic H). [^{13}C]NMR: 14·27 (C-4-CH_3), 22·35 (C-5-CH_3), 68·86 (C-5), 80·15 (C-4), 141·08 (C-1″). MS: m/z (%) = 347(24) [M^+].

3.1.8 trans-*5-(4-Chlorophenyl)-4,5-dimethylthiazolidin-2-one* (***6c***) *and* trans-*5-(4-chlorophenyl)-4,5-dimethylthiazolidine-2-thione* (***6d***)

A suspension of **7** (5·0 g, 14 mmol) in hydrochloric acid (6 M; 300 ml) was refluxed for 6 h. The solvent was removed under vacuum and the residue dissolved in a mixture of methanol (100 ml) and sodium hydroxide solution (2 M; 30 ml). The mixture was stirred at room temp. for 14 h, acidified with dilute hydrochloric acid, and then diluted with ether (300 ml). The precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography with hexane + ethyl acetate (7 + 3 by volume) as eluent to provide **6c** (1·81 g, 53%) and **6d** (0·8 g, 23%).

6c: m.p. 149–150°C. [^{1}H]NMR: 1·23 (d, J = 6 Hz, 3H, CH_3), 1·82 (s, 3H, CH_3), 4·21 (q, J = 6 Hz, 1H, CH), 6·3 (br.s, 1H, NH), 7·2–7·6 (m, 4H, aromatic H). MS: m/z (%) = 243(12) [M^+ + 2], 241(36) [M^+].

6d: m.p. 50°C. [^{1}H]NMR: 1·20 (d, J = 6 Hz, 3H, CH_3), 1·8 (s, 3H, CH_3), 4·52 (q, J = 6 Hz, 1H, CH), 7·2–7·6 (m, 4H, aromatic H), 8·05 (br.s, 1H, NH). MS: m/z (%) = 259 (11) [M^+ + 2], 257(33) [M^+], 194(61), 166(94), 151(62), 131(100), 115(64), 91(31).

3.2 Preparation of compounds 1b–1g, and 10a, b: General Procedure

To a stirred suspension of the appropriate oxazole or thiazole derivative **6a**–**6d** (4 mmol) in dry benzene (20 ml) was added dropwise cyclohexyl isocyanate (**8**) or phenyl isocyanate (**9**) (10 mmol) and the resulting mixture was stirred at room temperature for 72 h. An additional amount of isocyanate (10 mmol) was then added and the mixture was refluxed for 8 h. The solvent was evaporated under vacuum and the residue was purified by column chromatography with hexane + ethyl acetate (4 + 1 by volume) as eluent.

3.2.1 trans-*5-(4-Chlorophenyl)-4,5-dimethyl-2-thioxothiazolidine-3-carboxylic acid cyclohexylamide* (***1b***)

Yield: 50%, m.p. 110°C. [^{1}H]NMR: 1·1–2·0 (m, 10H, 5CH_2), 1·56 (d, J = 6 Hz, 3H, CH_3), 1·68 (s, 3H, CH_3), 3·66 (m, 1H, CH), 4·86 (q, J = 6 Hz, 1H, CH), 7·2–7·6 (m, 4H, aromatic H), 9·7 (br.s, 1H, NH). [^{13}C]NMR: 15·93 (C-4-CH_3), 22·90 (C-5-CH_3), 64·03 (C-4), 88·16 (C-5), 142·16 (C-1″).

3.2.2 trans-*5*-(*4-Chlorophenyl*)-*4,5-dimethyl-2-thioxothiazolidine-3-carboxylic acid phenylamide* (***1c***)
Yield: 62%, m.p. 102°C. [^{1}H]NMR: 1·52 (3, $J = 6$ Hz, 3H, CH_3), 1·62 (s, 3H, CH_3), 5·7 (q, $J = 6$ Hz, 1H, CH), 7·0–7·6 (m, 9H, aromatic H), 11·9 (br.s, 1H, NH).

3.2.3 trans-*5*-(*4-Chlorophenyl*)-*4,5-dimethyl-2-oxothiazolidine-3-carboxylic acid cyclohexylamide* (***1d***)
Yield: 94%, m.p. 121–122°C. [^{1}H]NMR: 1·0–2·0 (m, 10H, $5CH_2$), 1·54 (d, $J = 6$ Hz, 3H, CH_3), 1·68 (s, 3H, CH_3), 3·62 (m, 1H, CH), 5·12 (q, $J = 6$ Hz, 1H, CH), 7·32 (m-d, $J = 9$ Hz, 2H, C-3″-H and C-5″-H), 7·51 (m-d, $J = 9$ Hz, 2H, C-2″-H and C-6″-H), 7·93 (d, $J = 8$ Hz, 1H, NH). [^{13}C]NMR: 15·50 (C-4-CH_3), 57·45 (C-5), 62·83 (C-4), 143·86 (C-1″). MS: *m/z* (%) = 368(11) [$M^+ + 2$], 366(35) [M^+].

3.2.4 trans-*5*-(*4-Chlorophenyl*)-*4,5-dimethyl-2-oxothiazolidine-3-carboxylic acid phenylamide* (***1e***)
Yield: 88%, m.p. 128–129°C. [^{1}H]NMR: 1·59 (d, $J = 6$ Hz, 3H, CH_3), 1·70 (s, 3H, CH_3), 5·2 (q, $J = 6$ Hz, 1H, CH), 6·9–7·5 (m, 5H, aromatic H), 7·33 (m-d, $J = 9$ Hz, 2H, C-3″-H and C-5″-H), 7·52 (m-d, $J = 9$ Hz, 2H, C-2″-H and C-6″-H), 10·07 (br.s, 1H, NH). [^{13}C]NMR: 15·47 (C-4-CH_3), 24·81 (C-5-CH_3), 57·63 (C-5), 63·21 (C-4), 143·65 (C-1″). MS: *m/z* (%) = 362(9) [$M^+ + 2$], 360(27) [M^+].

3.2.5 trans-*5*-(*4-Chlorophenyl*)-*4,5-dimethyl-2-thioxooxazolidine-3-carboxylic acid cyclohexylamide* (***1f***)
Yield: 92%, m.p. 94–96°C. [^{1}H]NMR: 1·1–2·05 (m, 10H, $5CH_2$), 1·52 (d, $J = 6$ Hz, 3H, CH_3), 1·68 (s, 3H, CH_3), 3·65 (br.s, 1H, CH), 4·87 (q, $J = 6$ Hz, 1H, CH), 7·2–7·45 (m, 4H, aromatic H), 9·5 (m-d, $J = 7$ Hz, 1H, NH). [^{13}H]NMR: 15·39 (C-4-CH_3), 22·90 (C-5-CH_3), 64·03 (C-4), 88·16 (C-5), 142·13 (C-1″). MS: *m/z* (%) = 366(41) [M^+].

3.2.6 trans-*5*-(*4-Chlorophenyl*)-*4,5-dimethyl-2-thioxooxazolidine-3-carboxylic acid phenylamide* (***1g***)
Yield: 90%, m.p. 144–145°C. [^{1}H]NMR: 1·52 (d, $J = 6$ Hz, 3H, CH_3), 1·70 (s, 3H, CH_3), 4·95 (q, $J = 6$ Hz, 1H, CH), 7·0–7·6 (m, 9H, aromatic H), 11·62 (br.s, 1H, NH).

3.2.7 cis-*5*-(*4-Chlorophenyl*)-*4,5-dimethyl-2-thioxooxazolidine-3-carboxylic acid cyclohexylamide* (***10a***)
Yield: 92%, m.p. 96–97°C. [^{1}H]NMR: 0·91 (d, $J = 6$ Hz, 3H, CH_3), 1·1–2·1 (m, 10H, $5CH_2$), 1·77 (s, 3H, CH_3), 3·72 (m, 1H, CH), 4·78 (q, $J = 6$ Hz, 1H, CH), 7·2–7·5 (m, 4H, aromatic H), 9·65 (d, $J = 7$ Hz, 1H, NH). [^{13}H]NMR: 16·94 (C-4-CH_3), 27·23 (C-5-CH_3), 63·80 (C-4), 89·16 (C-5), 136·72 (C-1″). MS: *m/z* (%) = 366(40) [M^+].

3.2.8 cis-*5*-(*4-Chlorophenyl*)-*4,5-dimethyl-2-thiooxooxazolidine-3-carboxylic acid phenylamide* (***10b***)
Yield: 90%, m.p. 189–190°C. [^{1}H]NMR: 0·92 (d, $J = 6$ Hz, 3H, CH_3), 1·80 (s, 3H, CH_3), 4·85 (q, $J = 6$ Hz, 1H, CH), 7·1–7·7 (m, 9H, aromatic H), 11·80 (br.s, 1H, NH).

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